



Mitochondrial function controls proliferation and early differentiation potential of embryonic stem cells.

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## **Public Summary:**

Pluripotent stem cells hold significant promise in regenerative medicine due to their unlimited capacity for self-renewal and potential to differentiate into any cell type of the body. In this study, we demonstrate that proper mitochondrial function is essential for proliferation of undifferentiated ESCs. Attenuating mitochondrial function under self-renewing conditions makes these cells more glycolytic-dependent, and it is associated with an increase in the mRNA reserves of Nanog, Oct4, and Sox2. In contrast, attenuating mitochondrial function during the first 7 days of differentiation results in normal repression of Oct4, Nanog, and Sox2. However, differentiation potential is compromised as revealed by abnormal transcription of multiple Hox genes. Furthermore, under differentiating conditions in which mitochondrial function is attenuated, tumorigenic cells continue to persist. Our results, therefore establish the importance of normal mitochondrial function in ESC proliferation, regulating differentiation, and preventing the emergence of tumorigenic cells during the process of differentiation.

## **Scientific Abstract:**

Pluripotent stem cells hold significant promise in regenerative medicine due to their unlimited capacity for self-renewal and potential to differentiate into any cell type of the body. In this study, we demonstrate that proper mitochondrial function is essential for proliferation of undifferentiated ESCs. Attenuating mitochondrial function under self-renewing conditions makes these cells more glycolytic-dependent, and it is associated with an increase in the mRNA reserves of Nanog, Oct4, and Sox2. In contrast, attenuating mitochondrial function during the first 7 days of differentiation results in normal repression of Oct4, Nanog, and Sox2. However, differentiation potential is compromised as revealed by abnormal transcription of multiple Hox genes. Furthermore, under differentiating conditions in which mitochondrial function is attenuated, tumorigenic cells continue to persist. Our results, therefore establish the importance of normal mitochondrial function in ESC proliferation, regulating differentiation, and preventing the emergence of tumorigenic cells during the process of differentiation.

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